GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF RESEARCH ADMINISTRATION

RESEARCH PROJECT INITIATION

Date: November 10, 1971

Project Title: Organometallic Compounds. Mechanisms and Stereo-Chemistry of Reaction

Project No: G-33-640

Principal Investigator Dr. E. C. Ashby

Sponsor: National Science Foundation

Agreement Period: From November 1, 1971 Until April 30, 1973

Type Agreement: Grant No. GP-31550X

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7,862 GIT Contribution (Acct. G-33-333)
$39,662 Total Project Budget

Reports Required:
Annual Progress
Final (only if renewal support is not granted)

1 Sponsor Contact Person (s): Dr. Donald A. Speer, Director
Chemical Dynamics Program
National Science Foundation
Washington, D. C. 20550

Note: Continuation of Project No. G-33-614

Assigned to: School of Chemistr y

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RA-3 (6-71)

GEORGIA INSTITUTE OF TECHNOLOGY

OFFICE OF RESEARCH ADMINISTRATION

RESEARCH PROJECT TERMINATION

Date: June 4, 1970

Project Title: Organometallic Compounds. Mechanisms & Stereochemistry of Reaction

Project No: [illegible]

Principal Investigator: Dr. W. P. Ashby

Sponsor: National Science Foundation

Effective Termination Date: 4/7/71 (Grant expiration)

Clearance of Accounting Charges: by 4/30/71

Grant/Contract Closeout Actions Remaining: Final Fiscal Report (Office of Financial Affairs)

ASSIGNED TO [illegible] SCHOOL OF CHEMISTRY

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- Other _____

G-33-640

ANNUAL REPORT

E. C. Ashby

Mechanisms and Stereochemistry of Organometallic Addition Reactions

During the past year we have published five papers and presently have four in press describing the work carried out on the NSF program (list attached). It is probably worthwhile to point out that two of the papers in press are invited papers (Angewandte Chemie and Accounts of Chemical Research). Although these manuscripts are long enough and extensive enough to be considered review articles, they are both critiques covering (1) Stereochemistry of Organometallic Addition Reactions and (2) Mechanisms of Organometallic Addition Reactions.

During the past year we have worked on five projects, some of which have been completed and some of which are still in progress. Basically, everything that we are doing is directed toward developing a better understanding of exactly how main group organometallic compounds react with organic substrates. Once we understand these reactions sufficiently, we hope to be able to control and manipulate these reactions in ways heretofore unknown. We would not only like to control the reaction pathway in order to drive the reaction in a different direction (transition metal catalysis), but we would also like to control the stereochemical course of the reaction. A brief report on the five projects worked on during the past year directed to accomplish the above objectives follows.

We are continuing our studies concerning the importance of the purity of magnesium metal used to prepare Grignard reagents that are then allowed to react with organic substrates. We are attempting to determine

by ESR, UV and product studies whether single electron transfer is a fundamental process or an artifact of transition metal impurities in the magnesium metal. We are presently repeating the work of Holm and of Fauvarque using Grignard reagents prepared from single crystal magnesium.

We have completed our studies related to the evaluation of CH_3MgOR and CH_3MgNR_2 compounds (where R=n-Pr, i-Pr, t-Bu and Ph) as stereoselective alkylating agents towards ketones. As a result of this study we discovered a very interesting and we believe a very important reaction. We have found that dialkylamines can be degraded to monoalkylamines in high yield by a very convenient and rapid procedure.

$$(CH_3)_2Mg + HNR_2 \rightarrow CH_3MgNR_2 + CH_4$$

$$CH_3MgN(CH_2CH_2CH_3)_2 \rightarrow \left[\begin{array}{l} Mg\!-\!N(R) \\ CH_3 \quad CH_2 \\ H \quad C \quad H \\ \quad\quad CH_3 \end{array}\right] \rightarrow CH_4 + (MgNR)_n + CH_3\text{-}\overset{H}{C}\!=\!CH_2$$

There are two important aspects to this reaction (1) the preparation of $(MgNR)_n$ which maybe a polymer or a cyclic trimer. If it is a cyclic trimer, it would be the magnesium counterpart of borazole. The compound is soluble in THF and we are presently carrying out molecular weight and UV studies to determine this point. (2) This method provides a convenient, high yield route of converting R_2NH to RNH_2 compounds which could have considerable merit in structure illucidation by degradation. We would also like to study the stereochemistry of the reaction. We are assuming at this stage that the elimination is a cis stereospecific elimination.

We have recently completed a study involving the evaluation of "ate" complexes (e.g., $LiAl(CH_3)_4$, $Li_2Zn(CH_3)_4$, $KMg(CH_3)_3$, etc.) as stereoselective alkylating agents. The results are both interesting and informative.

We have also recently completed a study attempting to optimize the compression effect experienced in stereoselective alkylation of ketones by complexing the ketone with various Iewis acids (e.g., $i\text{-}Bu_3Al$, $AlCl_3$, $AlPh_3$, etc.). Once again, the results are both interesting and informative.

We have begun studies to evaluate the stereochemistry of 1,4-conjugate addition of organomagnesium and organoaluminum compounds to prostaglandin model systems. In this connection we are preparing 2-, 3- and 4-methylcyclopentenone. The stereochemistry of 1,4- conjugate addition is unknown and furthermore we plan to effect such addition by heretofore unexplored ways.

Papers Published During the Past Year (Sept. 1972-Sept. 1973)

1. H. M. Neumann, J. Laemmle, and E. C. Ashby, "Organometallic Reaction Mechanism. IX. Evidence for the Detailed Nature of the Alkyl Transfer Step in the Addition Reaction of Trimethylaluminum with Benzophenone," J. Amer. Chem. Soc., 95, 2597 (1973).

2. E. C. Ashby, H. M. Neumann, F. W. Walker, J. Laemmle, and Li-Chung Chao, "Organometallic Reaction Mechanisms. X. Concerning the effect of Magnesium Metal Purity and the Method of Preparation of Grignard Reagents on Reaction with Ketones and Nitriles," J. Amer. Chem. Soc., 95, 3330 (1973).

3. E. C. Ashby, Li-Chung Chao, and H. M. Neumann, "Organometallic Reaction Mechanism. XI. The Mechanism of Dimethylmagnesium Addition to Benzonitrile," J. Amer. Chem. Soc., 95, 5186 (1973).

4. E. C. Ashby, Li-Chung Chao, and H. M. Neumann, "Organometallic Reaction Mechanisms. XII. The Mechanism of Grignard Addition to Benzonitriles," J. Amer. Chem. Soc., 95, 4896 (1973).

5. J. Laemmle, E. C. Ashby and P. V. Roling, "Stereoselective Organometallic Alkylation Reactions. II. Organomagnesium and Organoaluminum Addition to Ketones Having Varied Steric Requirements. A New Concept of Stereochemical Control," J. Org. Chem., 38, 2526 (1973).

Papers in Press

1. G. E. Parris and E. C. Ashby, "The Composition of Grignard Compounds. IX. The Structure and Solution Composition of Cyclopentadienylmethylmagnesium in Benzene and Ether Solvents," J. Amer. Chem. Soc. (in press).

2. E. C. Ashby and John Nackashi, "The Preparation of Organomagnesium Fluorides by Organometallic Exchange Reactions," J. Organmetal. Chem., (in press).

3. E. C. Ashby and J. Laemmle, "Stereochemistry of Organometallic Compound Addition to Ketones," Angewandte Chemie, (in press).

4. E. C. Ashby and J. Laemmle and H. M. Neumann, "Mechanisms of Organometallic Compound Addition to Ketones and Nitriles," Accounts of Chemical Research, (in press).

Final Report

to the

National Science Foundation

January 13, 1975

Organometallic Compounds of the Main Group Elements. Composition, Mechanisms and Stereochemistry of Reaction

Grant No. GP - 31550X

E.C. Ashby, Regents' Professor of Chemistry

Georgia Institute of Technology

Table of Contents

ABSTRACT

For the past 3 years we have been concerned with four major projects: (1) the composition of organomagnesium compounds in ether solvents, (2) the kinetics and mechanisms of Grignard reagent addition to ketones and nitriles, (3) stereoselective alkylation of ketones employing new alkylating agents and (4) development of a new concept of stereochemical control. With respect to (1) we have defined by i.r., variable temperature nmr and molecular association studies the composition of $CpMgCH_3$, CH_3MgOR (where R = n-pr, i-pr, t-Bu and $Ph_2C(CH_3)\text{-})_3$ and CH_3MgNR_2 (where R = i-pr and Ph) compounds in ether solvent. With respect to (2) we have reported detailed mechanisms of the reactions of $(CH_3)_2Mg$ and methyl bromide Grignard reagent with 2-methylbenzophenone and benzonitrile. We have also determined the importance of magnesium metal purity (used to prepare Grignard reagents) to the reaction pathway whereby Grignard reagents react with ketones and nitriles. The detailed nature of alkyl transfer in organoaluminum addition to ketones has also been reported. With respect to (3) "ate" complexes and RMgX (where X = OR and NR_2) compounds have been evaluated as stereoselective alkylating agents towards ketones and with respect to (4) we have described a new concept of stereochemical control which explains all our observations concerning organoaluminum and organomagnesium addition to ketones. During the report period, 19 papers have been published concerning the above work and 2 are in press.

A. Composition of Organomagnesium Compounds in Ether Solvents

(1) Grignard Compounds

Our studies concerning the composition of Grignard compounds and other organomagnesium compounds is essentially complete. Our entire findings in the area of Grignard reagent composition can be found in the recent paper entitled, "The Composition of Grignard Compounds in Ether Solvents as Inferred from Molecular Association and NMR Studies", Bull. Soc. Chemie de France, 2133 (1972). The combination of molecular association and NMR studies seems to provide the kind of information needed to establish the nature of the complex equilibria in solution.

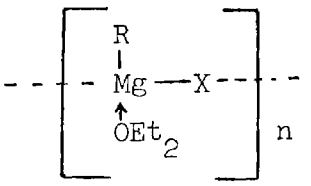
A summary of results are as follows:

Et_2O Solvent

The composition of Grignard compounds in ether solvent can be described by the equilibria below.

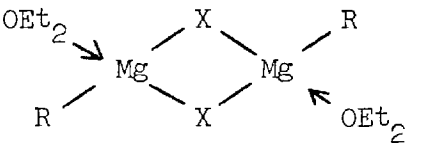
$$\text{Associated Species} \rightleftharpoons R_2Mg + MgX_2 \overset{K_1}{\rightleftharpoons} 2\ RMgX \rightleftharpoons \text{Associated Species}$$

When X = Br and I, the RMgX species are associated in a linear polymeric fashion (A) whereas when X = Cl or F, the RMgX species are dimeric (B)



(A)

X = Br, I



(B)

X = Cl, F

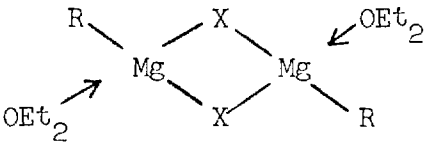
over a wide concentration range. At 0.1 M concentration or lower, n = 1 when X = Br or I; however, the value of n increases with concentration in an almost linear fashion so that at 2 M concentration or greater, $n > 3$. K_1 is large (~ 400) when X = Br or I and R is alkyl; however,

when R is aryl the value of K_1 is in the range 10-50. NRM was able to distinguish between R_2Mg and RMgX species in an ether solution of methyl-and t-butylmagnesium bromide, thus resolving for the first time by direct spectroscopic observation, the question concerning the existence of RMgX species in solution.

THF Solvent

In THF solvent all Grignard, dialkyl- and diarylmagnesium compounds are monomeric except fluoro Grignard compounds which are dimeric. The value of K = 4 represents a statistical distribution of species.

$$R_2Mg + MgX_2 \overset{K}{\rightleftharpoons} 2\ RMgX \qquad (X = Cl, Br, I)$$



(X = F)

Et_3N Solvent

Grignard, dialkylmagnesium and magnesium halide compounds where X = Cl, Br or I are monomeric in Et_3N. The composition of Grignard compounds in Et_3N can be expressed by the Schlenk equilibrium.

$$R_2Mg + MgX_2 \rightleftharpoons 2\ RMgX$$

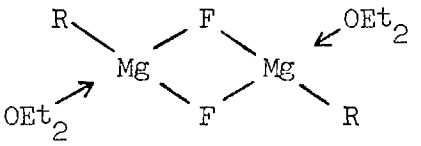
The equilibrium lies predominantely to the right when R is a 1° alkyl group and X = Cl. When R is a 2° or 3° alkyl group and X = Br or I, detectable amounts of R_2Mg and MgX_2 are present.

A separate publication entitled, "The Preparation of Alkylmagnesium Fluorides," J. Org. Chem., 36, 2123 (1972) describes the preparation of fluoro Grignard reagents from alkyl fluorides and

magnesium in THF or DME. Although this preparative route to Grignard

$$RF + Mg \rightarrow RMgF$$

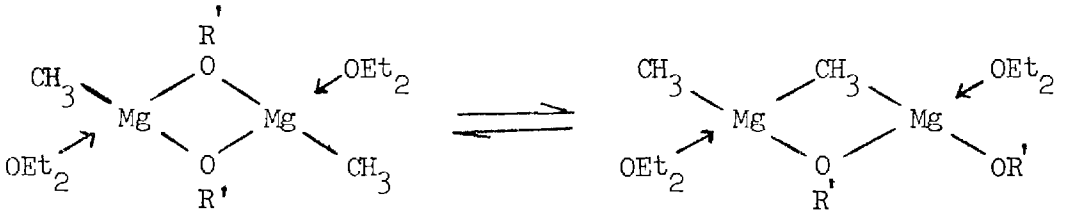
reagents is well known when the halogen is Cl, Br or I, the literature reports that the reaction does not take place when X = F. However, in THF or DME using activated magnesium metal, the reaction proceeds to form the fluoro Grignard compound in > 90% yield in 4 hours under the conditions of DME reflux. "The Composition of Grignard Compounds. VIII. Alkylmagnesium Fluorides", J. Organometall. Chem., 29, 339 (1971), establishes the unique composition of fluoro Grignard compounds by molecular association, ir and nmr studies. In Et_2O and THF, regardless of the nature of the alkyl group or the concentration of the solution, the reagent appears to exist as a double fluorine bridged dimer.



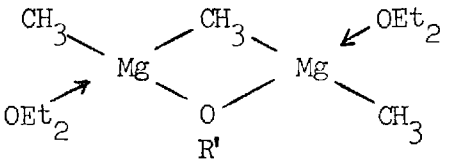
(2) RMgX Compounds (where X = OR and NR_2) in Ether Solvent

A series of CH_3MgOR' compounds have been prepared (where R' = n-propyl-, i-propyl, t-butyl- and $Ph_2C(CH_3)$-. The composition of these compounds in ether solvent has been studied by molecular association and variable temperature nmr and has been found to be a function of the nature of the alkoxy group. All compounds are dimeric at low concentration and associate at higher concentrations. The degree of association is least with the bulky groups [$OCPh_2(CH_3)$] and greatest with the 1° alkoxy compounds ($OCH_2CH_2CH_3$). Variable temperature nmr studies have established

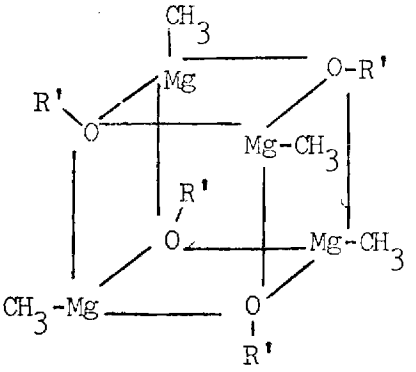
the existence of a mixed methyl-alkoxy bridge species.



The above equilibrium lies predominantely to the left; however, when an equal molar amount of $(CH_3)_2Mg$ is added to the CH_3MgOR' compound, the predominant species in solution is a mixed methyl-alkoxy bridged compound.



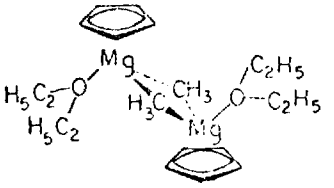
We have recently found that the composition of CH_3MgOR' compounds change with time. The kinetically controlled product in an open chain equilibrium mixture of dimer, trimer, tetramer, etc., whereas with heating or after sublimation, a thermodynamically favored cubane tetramer is formed.



CH_3MgNPh_2 and $CH_3MgN(Pr^i)_2$ have been prepared and their composition in solution studied by molecular association and variable temperature nmr. CH_3MgNPh_2 is monomeric in Et_2O and does not form a complex with $(CH_3)_2Mg$. On the other hand, $CH_3MgN(Pr^i)_2$ does form a complex mixture of mixed bridged species. An initial report on this work can be found in J. Organometal. Chem., 35, C1 (1972).

(3) Cyclopentadienylmethylmagnesium in Benzene and Ether Solvent

The composition of $C_5H_5MgCH_3 \cdot OEt_2$ has been studied by molecular association, variable temperature nmr and infrared analysis. Comparrison of its infrared spectrum with $(CH_3)_2Mg$ and $(C_5H_5)_2Mg$ indicates that in the solid state the magnesium atoms are associated via methyl bridge bonds and that the cyclopentadienyl ring has approximately D_5h symmetry.



When dissolved in benzene, the methyl bridge bonds are retained; however, partial dissociation of the ether occurs. On the other hand,

$$[C_5H_5MgCH_3 \cdot OEt_2]_2 \rightleftharpoons (C_5H_5MgCH_3)_2 \cdot OEt_2 + OEt_2$$

polar solvents, such as Et_2O and particularly THF cleave the methyl bridge bonds.

$$[C_5H_5MgCH_3 \cdot OEt_2]_2 + 2\ Et_2O \rightleftharpoons C_5H_5MgCH_3 \cdot 2Et_2O$$

This work has been completed and has been published in the Journal of Organometallic Chemistry 72, 1 (1974).

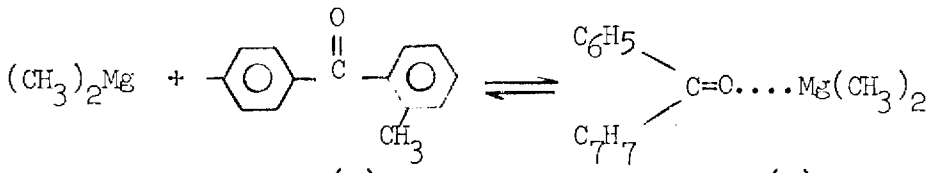
B. Mechanisms of Grignard and Dialkylmagnesium Compound Addition to Organic Substrates

(1) Dimethylmagnesium Addition to 2-Methylbenzophenone

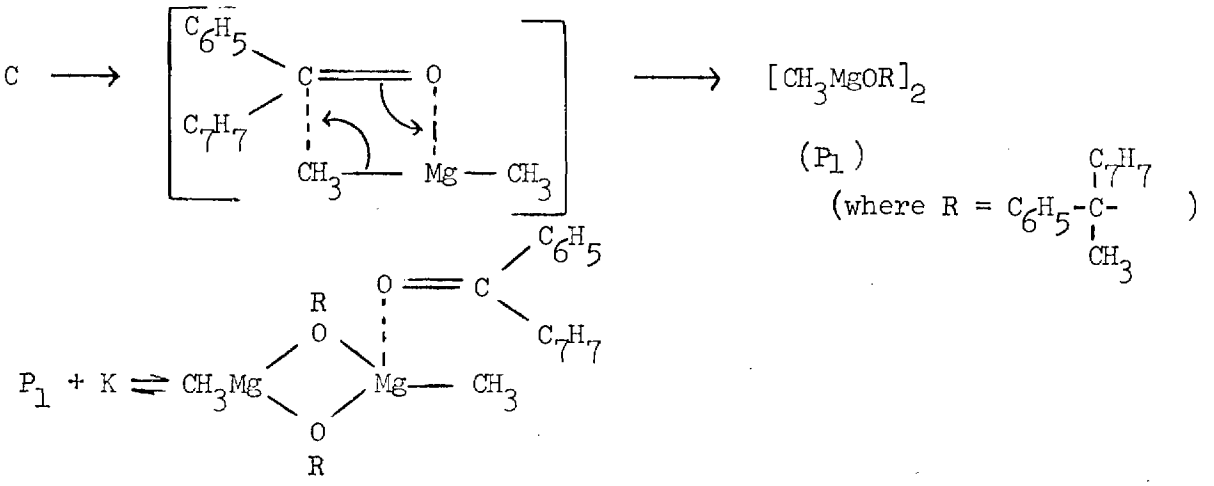
The kinetics of the reaction of $(CH_3)_2Mg$ with excess 2-methylbenzophenone was followed spectroscopically by observing the disappearance of an absorption band attributed to a complex of $(CH_3)_2Mg$ with the ketone and by directly observing the appearance of the product. By using a large excess of ketone, the kinetic order of the organomagnesium species was determined unambiguously to be first order. The reaction of $(CH_3)_2Mg$ with excess ketone was found to consist of a series of pseudo-first-order reactions involving the formation of two intermediate products prior to the formation of the final product.

$$\text{reactants} \longrightarrow P_1 \xrightarrow{\text{ketone}} P_2 \xrightarrow{\text{ketone}} P_3 \text{ (final product)}$$

Quenching studies at definite intervals during the reaction established the formulas of P_1, P_2, and P_3 to be $[CH_3MgOR]_2$, $[CH_3MgOR \cdot Mg(OR)_2]$, and $[Mg(OR)_2]$, respectively (where R = $C(C_7H_7)(C_6H_5)CH_3$). Complexes between the ketone and P_1 and P_2 were observed spectroscopically. The kinetic data can be interpreted in terms of the reaction proceeding through complex formation between the ketone and the organomagnesium species, or in terms of a bimolecular collision not involving the complex. A detailed description of the proposed mechanism is as follows.

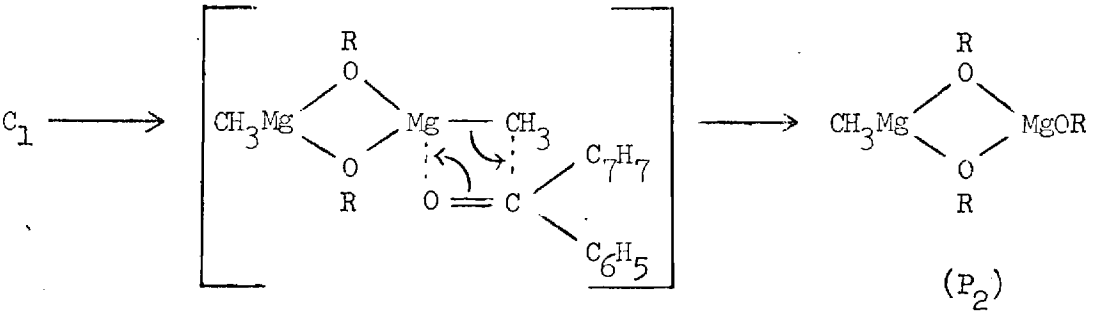


(K) (C)

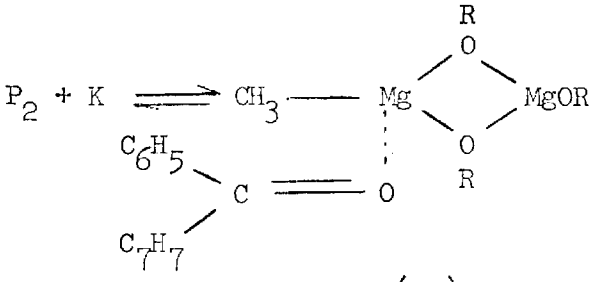


(P_1) (where R = $C_6H_5-C(CH_3)(C_7H_7)-$)

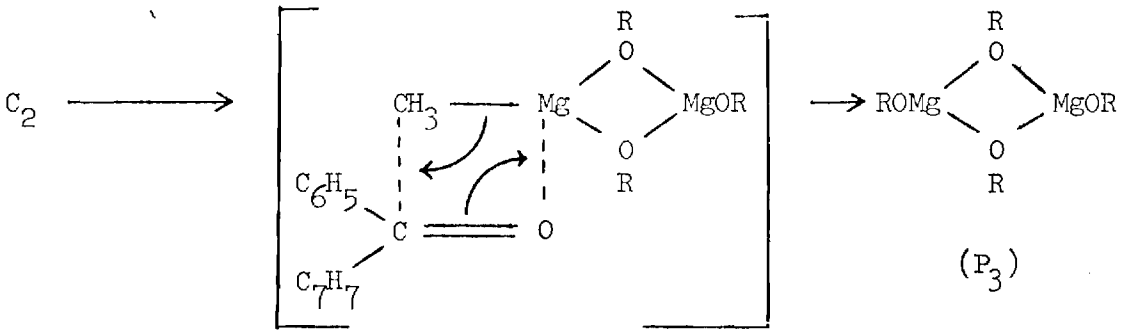
(C_1)



(P_2)



(C_2)



The mechanism of $(CH_3)_2Mg$ addition to ketones is important because the Grignard reagent is a mixture of R_2Mg and RMgX species, both of which are alkylating species (J. Amer. Chem. Soc., 93, 5120 (1971).

(2) Mechanism of Methyl Bromide Grignard Addition to Ketones

The major areas of dispute concerning the mechanism of Grignard reagent addition to ketones have been the establishment of the reaction order of the Grignard reagent, the role of the reactive species (RMgX or R_2Mg), and the inability to evaluate kinetic data because of the presence of free ketyl in the reaction resulting in the formation of pinacol by-product. We have arrived at satisfying answers to all of these questions for the reaction of methylmagnesium bromide with 2-methylbenzophenone. We have determined the reaction order of the Grignard reagent unequivocally by carrying out kinetic studies in excess ketone. The reaction proceeds by two paths, one first-order in CH_3MgBr and the other first-order in $(CH_3)_2Mg$. The integral order behavior of the CH_3MgBr species was established by addition of sufficient $MgBr_2$ to the Grignard solution to shift the Schlenk equilibrium in the direction of this species.

$$(CH_3)_2Mg + MgBr_2(XS) \rightleftharpoons 2\ CH_3MgBr$$

The integral order behavior of the $(CH_3)_2Mg$ species was determined by simply studying the kinetics of the reaction using only $(CH_3)_2Mg$ as described in the previous section.

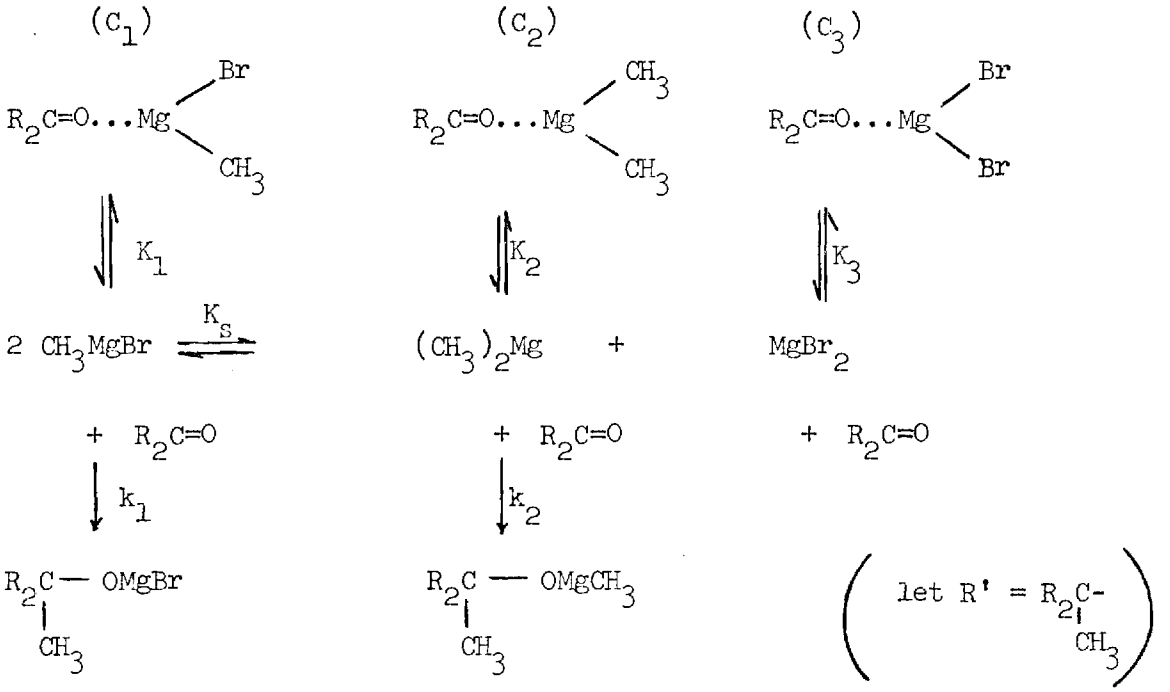
It was found that in the initial stages of the reaction both $(CH_3)_2Mg$ and CH_3MgBr participate in the alkylation to comparable degrees. This is a result of the fact that $(CH_3)_2Mg$ reacts about 10 times faster than the CH_3MgBr species; however, there is 10-15 times more CH_3MgBr present than $(CH_3)_2Mg$ in the Grignard solution. Although the reaction becomes more complicated beyond its initial stage, kinetic data from a variety of experiments revealed the series of steps and the nature of the intermediates that lead to the final product. Exchange studies involving magnesium bromide with all possible products arising from the reaction of ketone with dimethylmagnesium, i.e., $(ROMgCH_3)_2$, $(ROMgCH_3 \cdot ROMgBr)$, show that these species have but fleeting existence in the reaction. Thus, the complexity is caused solely by the interaction of the product of CH_3MgBr addition to ketone, ROMgBr, with the species CH_3MgBr, $(CH_3)_2Mg$ and $MgBr_2$, and their respective ketone complexes. An overall reaction scheme follows.

$$G + K \longrightarrow \text{product} \underset{[G]}{\rightleftharpoons} G \cdot P \xrightarrow[k_4]{[\text{ketone}]} \text{product}$$

$$\text{product} \underset{[G]}{\rightleftharpoons} G \cdot P_2 \xrightarrow[k_5]{[\text{ketone}]} \text{product}$$

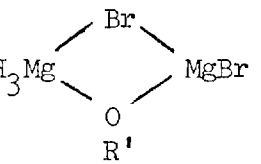
The amount of free 2-methylbenzophenone ketyl formed in the reaction is apparently very small since product studies under the actual conditions of the kinetics gave 100% yields of addition product. In addition, uv analysis shows that the rate of formation of the ketyl

is much slower than the rate of alkylation. With all of these factors in mind a detailed mechanism describing the reaction of methyl bromide Grignard reagent with 2-methylbenzophenone was suggested; this mechanism follows.



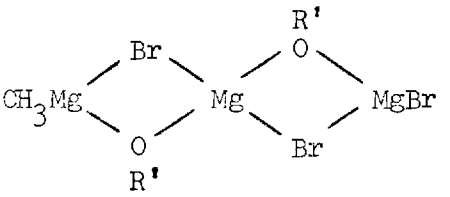
$$R'OMgCH_3 + MgBr_2 \rightleftharpoons R'OMgBr + CH_3MgBr$$

$$(R'OMgBr)_2 + 2\ CH_3MgBr \rightleftharpoons 2$$



(G·P)

$$(R'OMgBr)_2 + CH_3MgBr \rightleftharpoons$$



$(G \cdot P_2)$

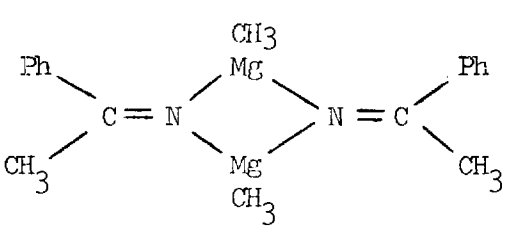
$$G\cdot P + R_2C{=}O \rightleftharpoons C$$
$$\downarrow k_4$$
$$(R'OMgBr)_2$$

$$G\cdot P_2 + R_2C{=}O \rightleftharpoons C$$
$$\downarrow k_5$$
$$3/2\ (R'OMgBr)_2$$

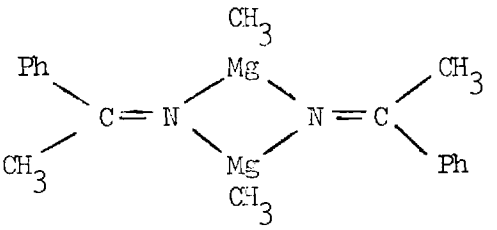
Since single electron transfer is a function of the nature of the R group of the Grignard reagent, the solvent, the ketone and the purity of the magnesium used to prepare the Grignard reagent, this mechanism is suggested only for the particular system studied. Further work will be required to distinguish S.E.T. from a polar mechanism and the conditions under which each type of mechanism is observed. Suggestions for these studies are presented in the section entitled, "Proposed Research". A detailed description of the above work can be found in J. Amer. Chem. Soc., 94, 5421 (1972).

(3) Mechanism of $(CH_3)_2Mg$ Addition to Benzonitrile

The reaction of dimethylmagnesium with benzonitrile in diethyl ether at 25° was examined in detail. Kinetic studies carried out under pseudo-first-order conditions using either excess dimethylmagnesium or excess nitrile were successful in determining the integral order behavior of both the dimethylmagnesium and the benzonitrile. The reaction was found to be first-order in benzonitrile and first-order in dimethylmagnesium. The product of the reaction was shown to be a mixture of cis and trans compounds in a 1:8 ratio.

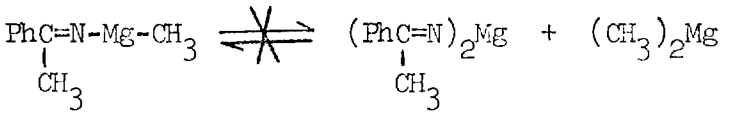


(cis)

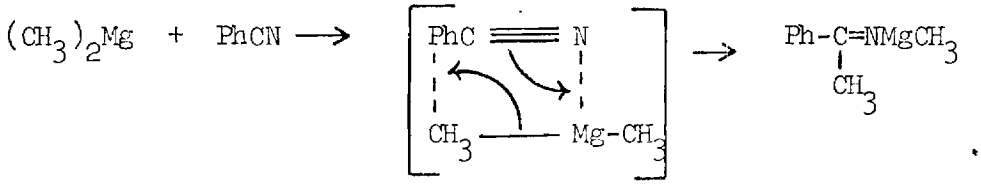


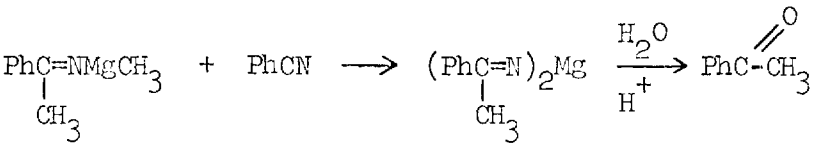
(trans)

The kinetic studies in excess $(CH_3)_2Mg$ show that PhCN and $(CH_3)_2Mg$ react to form $PhC(CH_3)NMgCH_3$ in quantitative yield with no evidence of redistribution.



Kinetic studies in both excess $(CH_3)_2Mg$ or PhCN indicate the following mechanism. (A detailed description of this work can be found in, J. Amer. Chem. Soc., 94, 5186 (1972)).





In the presence of a large excess of PhCN and at high concentration, substantial amounts of condensation products are produced in addition to

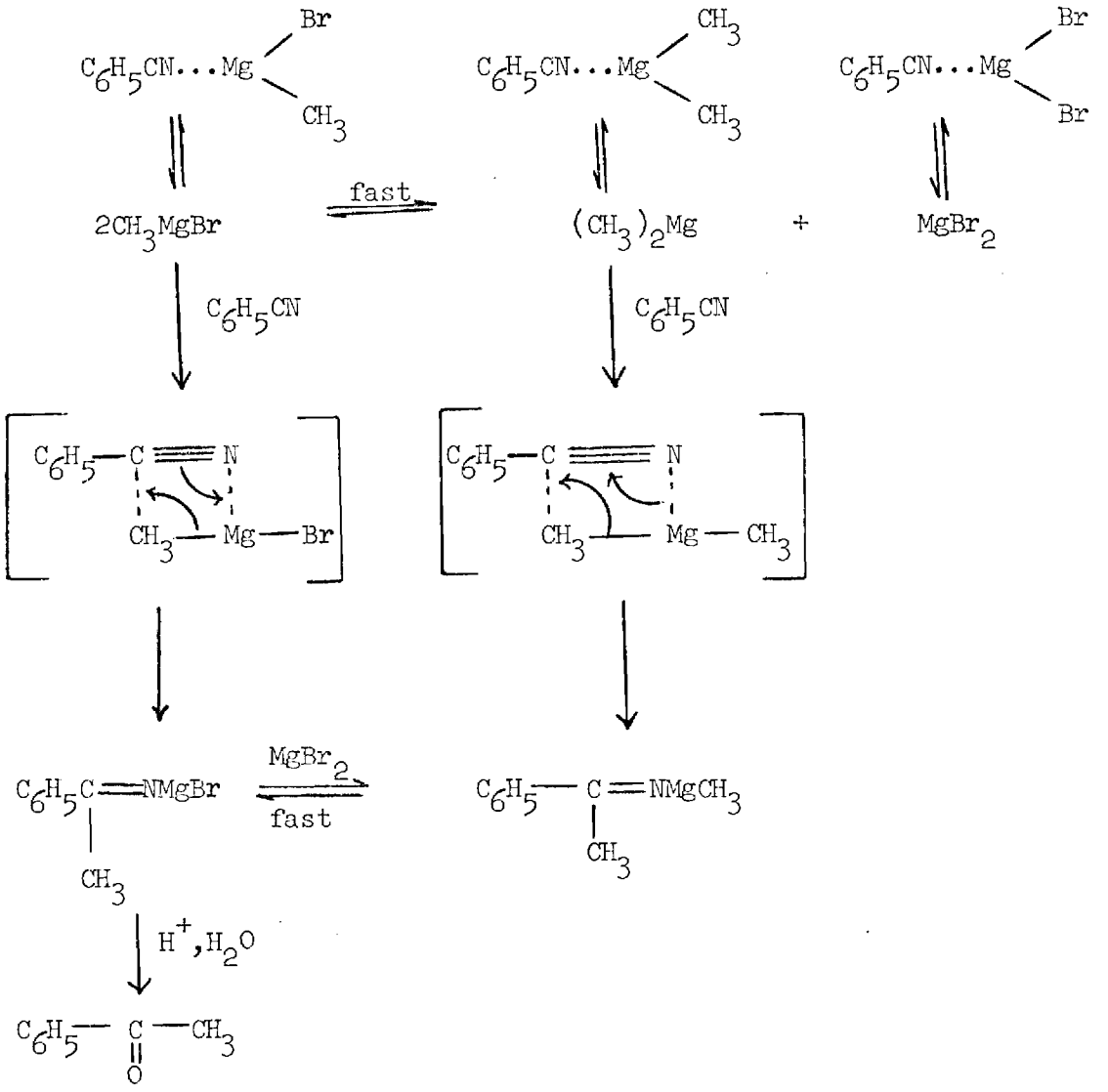
the products produced in the sequence of reactions shown above.

$$C_6H_5\underset{\underset{CH_3}{|}}{C}{=}NMgCH_3 + PhCN \xrightarrow[\text{large excess PhCN}]{\text{high concentration}} \text{Condensation Product I}$$

$$\text{Condensation Product I} \xrightarrow[\text{large excess PhCN}]{\text{high concentration}} \text{Condensation Product II}$$

(4) Mechanism of Methyl Bromide Grignard Addition to Benzonitrile

The kinetics of the reaction of methylmagnesium bromide with benzonitrile in diethyl ether was examined in detail in both excess Grignard reagent and excess nitrile. The reaction was found to produce, on hydrolysis, the alkylation product acetophenone in quantitative yield when the Grignard reagent was prepared from single crystal magnesium. The kinetic data of the reaction show a second-order reaction, first-order in Grignard reagent and first-order in nitrile. The results of rate studies in the presence of added $MgBr_2$ show that the reaction of the Grignard reagent with benzonitrile occurs through both the $(CH_3)_2Mg$ and CH_3MgBr species. All of the accumulated information is consistent with a mechanism which follows two reaction paths. One path involves reaction of benzonitrile with CH_3MgBr species, whereas the other path involves reaction of benzonitrile with $(CH_3)_2Mg$ to form $C_6H_5C(CH_3)NMgCH_3$ which subsequently and rapidly redistributes with $MgBr_2$ to form the final product $C_6H_5C(CH_3)NMgBr$ and methylmagnesium bromide. The detailed mechanism of the reaction is as follows.



A detailed description for this work can be found in J. Amer. Chem. Soc., 94, 4896 (1972).

(5) Effect of Magnesium Metal Purity and Method of Preparation of Grignard Reagents on the Reactions of Grignard Reagents with Ketone and Nitriles

Reports concerning the addition of Grignard reagents to ketones have not provided satisfactory explanations for the following points:

(1) the relationship between by-product formation and the behavior of the pseudo-first-order rate constants, (2) the relationship between by-product formation and normal addition, (3) the role played by the impurities in the magnesium used in the Grignard reagent preparation with respect to by-product formation and erratic rate behavior, and (4) the role played by the manner in which the Grignard reagents is prepared, i.e., employing excess magnesium or excess alkyl halide, with respect to by-product formation and erratic rate behavior. With respect to the latter two points, we reported in our last proposal that methylmagnesium bromide prepared from triply sublimed magnesium employing an excess of methyl bromide drastically reduces the per cent of by-product formation (20 to 6%) in benzophenone alkylation compared to methylmagnesium brmoide prepared using excess triply sublimed magnesium. In addition methylmagnesium bromide prepared from ultrapure magnesium employing an excess of methyl bromide essentially eliminated by-product formation and ketone concentration dependence on the pseudo-first-order rate constants in benzophenone alkylation. The study carried out here differs from previous reports in several respects. The reaction of benzophenone with large excesses of methylmagnesium bromide was investigated. The Grignard reagents were prepared from several sources of magnesium employing both excess magnesium and excess methyl bromide. Pseudo-first-order rate constants were recorded for several ketone concentrations at constant methylmagnesium bromide concentration of each Grignard reagent. In addition, samples from the actual kinetic runs were quenched at infinite time and the extent of by-product formation was determined. This allowed us to relate the variation of

pseudo-first-order rate constant to the extent of by-product formation. In addition to benzophenone, the behavior of methylmagnesium bromide with excess 2-methylbenzophenone and with benzonitrile was also studied. A summary of the results of this study is provided in the two tables that follow.

The reaction of methylmagnesium bromide with benzophenone under pseudo-first-order conditions (in excess methylmagnesium bromide) gives rate constants which are dependent on the initial ketone concentration and also gives significant amounts of nonaddition products. These effects are significantly reduced when the purity of the magnesium used to prepare the Grignard reagent is increased. For example, when the Grignard reagent was prepared by using excess doubly sublimed magnesium and the reaction carried out in a Grignard:Ketone ratio of 470, only 73% addition product was observed. On the other hand, when the same Grignard reagent was prepared in excess methyl bromide, and the reaction carried out at the same Grignard:Ketone ratio,the yield was 92%. The corresponding yields using a Grignard reagent prepared from single crystal magnesium was 88 and 95%, respectively.

Since the Grignard prepared from excess doubly sublimed magnesium gave 73% addition and from excess single crystal magnesium gave 88% addition, it is clear that both magnesium metal purity is important as well as the manner of preparation of the Grignard reagent, i.e., whether it is prepared in excess magnesium or excess methyl bromide. Similar results were obtained using benzonitrile as the substrate. It is clear that both magnesium metal purity and the manner in which the Grignard reagent is prepared are important factors in the reaction of Grignard reagents with nitriles as well as ketones. More detailed

Product Analysis and Pseudo-First-Order Constants from the Reaction of Methylmagnesium Bromide with Benzophenone in Diethyl Ether at 25°

Source of Magnesium	Grignard prepared with excess	$[G]_o/[K]_o$	$k_{obsd}/[G]_o$	% addition
Doubly sublimed	Mg	470	2.28	72.7
	Mg	112	1.40	84.6
	Mg	57	1.23	91.9
	CH_3Br	487	1.29	92.2
	CH_3Br	117	1.07	96.9
	CH_3Br	60	1.00	98.1
Single crystal	Mg	467	1.63	88.1
	Mg	112	1.33	94.6
	Mg	57	1.25	96.3
	CH_3Br	479	1.38	95.0
	CH_3Br	115	1.23	97.9
	CH_3Br	58	1.17	98.1

Product Analysis and Pseudo-First-Order Constants from the Reaction of Methylmagnesium Bromide with Benzonitrile in Diethyl Ether at 25°

Source of magnesium	Grignard prepared with excess	$[G]_o/[N]_o$	$k_{obsd}/[G]_o$	% addition
doubly sublimed	Mg	186	3.46	88.3
	Mg	62	3.03	95.8
	Mg	37	2.60	98.6
	CH_3Br	179	5.30	100
	CH_3Br	60	3.35	100
	CH_3Br	36	2.56	100
single crystal	Mg	181	2.91	98.0
	Mg	61	2.44	99.6
	Mg	36	2.47	99.6
	CH_3Br	181	2.86	100
	CH_3Br	61	2.71	100
	CH_3Br	36	2.61	100

information concerning this work can be found in, J. Amer. Chem. Soc., 95, 3330 (1973).

(6) The Detailed Nature of the Alkyl Transfer Step in the Reaction of $(CH_3)_3Al$ with Benzophenone

A study of the kinetics of addition of trimethylaluminum to benzophenone in benzene has been carried out. The reaction in benzene was found to proceed through two distinct mechanistic paths depending on the ratio of reactants. In this solvent, the reactants, $Al(CH_3)_3$ and ketone, form a complex whose formation is nearly complete. When the ratio of $Al(CH_3)_3$ to ketone is 1:1 or less, the product is formed by a relatively slow rearrangement of the complex. When this ratio is greater than 1:1, rapid formation of product results from attack on the complex by a second molecule of monomeric trimethylaluminum. The half-life of the complex is about 2900 sec when it is present alone at 0.0883 M concentration, but decreases to about 50 sec when trimethylaluminum is also present at the same concentration.

A major unresolved area concerning alkylation of ketones by organometallic compounds is the exact nature of the alkyl transfer step. In reactions in which the transition state has the same composition as the complex, the question is whether reaction occurs by direct intramolecular rearrangement of complex or by bimolecular collision involving the initially separated species. It is impossible to distinguish between the two reaction paths on the basis of kinetics since the mathematical expressions describing both cases are essentially the same. The reaction of trimethylaluminum with benzophenone in a 1:1 ratio in benzene where the reactants are initially present almost

completely as complex, and in diethyl ether, where the reactants are initially present almost totally as separated species, afforded a unique opportunity for the study of this unresolved aspect of organometallic reaction mechanisms. An added incentive to carry out this study was based on the unusual observation that the stereochemistry of addition of $(CH_3)_3Al$ to substituted cyclohexanones and cyclopentanones is significantly changed as the $(CH_3)_3Al$:ketone ratio is varied from 1:1 to 2:1.

Rate data for the addition of trimethylaluminum to benzophenone at several ratios and at several temperatures in diethyl ether were obtained, and the activation parameters for each case calculated. Critical examination of the activation parameters for diethyl ether and the 1:1 reactant ratio in benzene indicate a common transition state, which arises from the reactants being held in a solvent cage, followed by bimolecular reaction of trimethylaluminum with the ketone. The reaction of excess trimethylaluminum with benzophenone in benzene proceeds via a different transition state; the activation parameters indicate a rigid cyclic transition state.

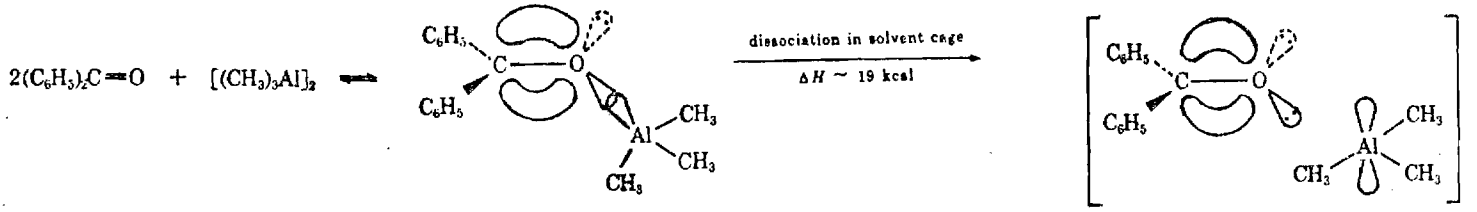
Activation Parameters for the Addition of Trimethylaluminum to Benzophenone in Benzene in a 1:1 Reactant Ratio

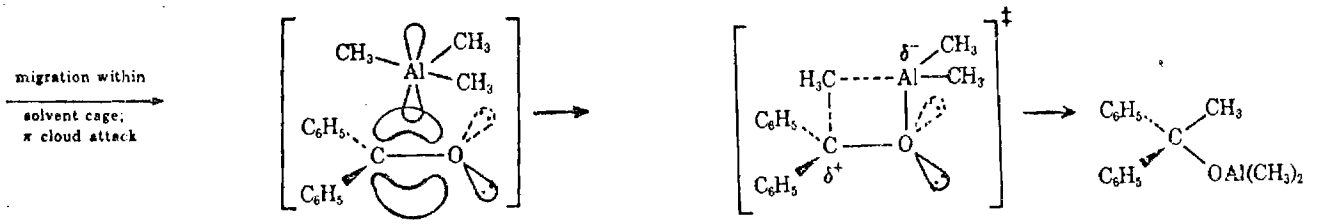
Temp, °C	$10^4 k$, sec^{-1}	
12.6	0.316	E_a = 19.1 kcal
20.0	0.607	Frequency factor = 1.27×10^{10} l. mol sec^{-1}
25.0	1.20	
30.0	2.07	$\Delta H^{\ddagger}$ = 18.5 kcal
40.0	5.95	$\Delta S^{\ddagger}$ = 14.1 eu

Activation Parameters for the Addition Reaction of Trimethylaluminum to Benzophenone in Diethyl Ether

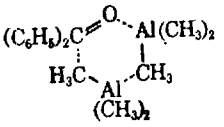
Temp, °C	10^6k, l. mole^{-1} sec^{-1}	
0.0	0.123	E_a = 22.8 kcal
20.0	2.19	Frequency factor = 2.22 x 10^{11} l. mole sec^{-1}
25.0	4.14	$\Delta H^{\ddagger}$ = 22.2 kcal
30.0	7.88	$\Delta S^{\ddagger}$ = -8.6 eu

The suggested mechanism for the reaction in 1:1 ratio involves initial rapid complex formation, followed by a rate determing dissociation of the complex, followed by a rapid alkyl transfer to form the product.

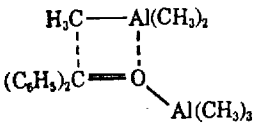




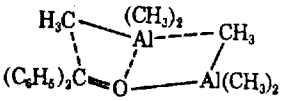
When the reaction is carried out in 2:1 ratio [$(CH_3)_3Al$:ketone], the initial step involves rapid complex formation followed by a rate determining step involving attack on the complex by an additional molecule of $(CH_3)_3Al$. Whether the rate determining step proceeds via a cyclic 6-center transition state (D) or a 4-center transition state (E) is not certain; however, a detailed analysis of both transition states indicates little difference between the two (F).



(D)



(E)



(F)

A more detailed discussion of this work can be found in, J. Amer. Chem. Soc., 95, 2597 (1973).

C. Stereochemistry of Organometallic Addition Reactions

(1) Stereochemistry of Aluminum Alkyl Addition to Ketones. A New Concept of Stereochemical Control

We have just discussed the fact that the reaction of $(CH_3)_3Al$ and benzophenone in a 1:1 ratio involves a transition state containing one molecule of $(CH_3)_3Al$ and one molecule of ketone. The reaction occurs through the initial formation of a complex followed by the rate determining formation of a 4-center transition state. On the other hand, when $(CH_3)_3Al$ and benzophenone were allowed to react in a 2:1 or greater ratio, it was found that the transition state describing the rate-determining step contains two molecules of $(CH_3)_3Al$ one one molecule of ketone. The mechanism of this reaction is envisioned

as attack of a molecule of $(CH_3)_3Al$ on the 1:1 complex, possibly *via* a 6-center transition state, to form the product. In light of the fact that two different mechanisms are operating in these two cases, a decision was made to study the reaction of $(CH_3)_3Al$ with 4-*t*-butylcyclohexanone in 1:1 and 2:1 ratio in benzene. It was not surprising to find a difference in the stereochemistry of the reactions at the two different ratios; however, such a dramatic change in the stereochemistry was surprising. In 1:1 ratio ~ 75% equatorial attack of the ketone took place whereas in 2:1 ratio the stereochemistry was completely reversed resulting in ~ 90% axial attack.

Close scrutiny of molecular models depicting 4- and 6-center transition states does not readily reveal the reason for the unusual stereochemistry found in the reaction of $(CH_3)_3Al$ and 4-*tert*-butylcyclohexanone in hydrocarbon solvent. From a steric point of view, axial attack on a chair conformation should be hindered by the 3 and 5 axial substituents regardless of whether the transition state is 4- for 6-center. It is conceivable that cyclohexanones complexed to aluminum alkyls exist in conformations other than chairs (such as a boat), or other factors, not yet considered, might be important. In order to resolve the speculation surrounding this unusual stereochemical observation, a comprehensive study of the reaction of aluminum alkyls and aryls with several ketones was undertaken. The reactions of Me_3Al, Et_3Al and Ph_3Al with 4-*t*-butylcyclohexanone in both benzene and ether were studied and the results are reported in the table below.

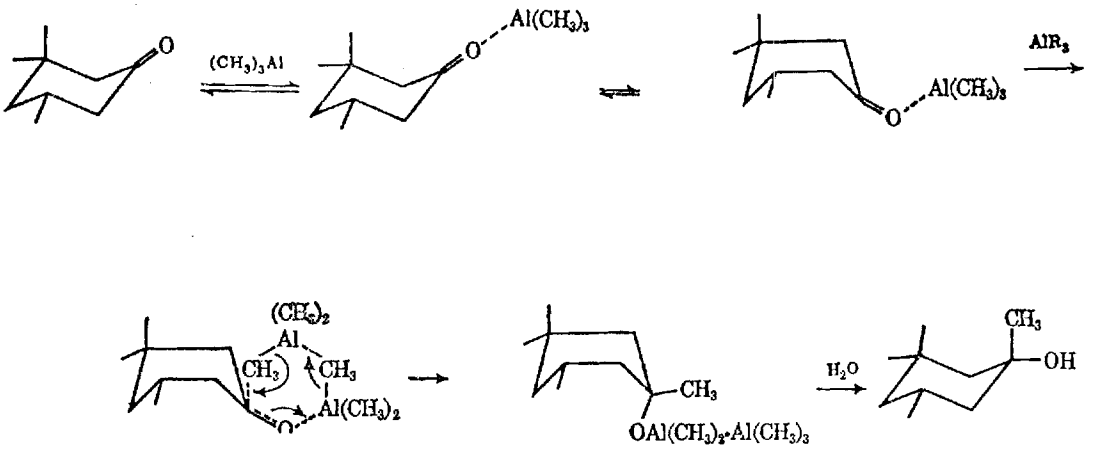
Reaction of Organoaluminum Compounds

with 4-tert-Butylcyclohexanone

AlR_3	Solvent	Ratio of AlR_3/Ketone	% Equatorial Attack
$(CH_3)_3Al$	Benzene	0.5	80
	"	1.0	76
	"	1.5	53
	"	2.0	17
	"	3.0	12
$(C_2H_5)_3Al$	"	1.0	88
	"	2.0	17
	"	4.0	14
$(C_6H_5)_3Al$	"	1.0	51
	"	2.0	27
	"	4.0	8
$(CH_3)_3Al$	Et_2O	1.0	85
	"	3.0	87
$(C_2H_5)_3Al$	"	1.0	88
	"	3.0	88
$(C_6H_5)_3Al$	"	1.0	44
	"	3.0	44

The results show in each case a profound change in stereochemistry when R_3Al:ketone ratio changes from 1:1 to 2:1 in benzene solvent, but not ether. In the 2:1 cases in benzene the ketone is being attacked predominantely from the most hindered side. This result could be explained by the reaction proceeding in the 2:1 case through the boat conformation (shown below); however, the data that follows involving 3,3,5-trimethyl-

cyclohexanone indicates that this is not the case.



Reaction of Organoaluminum Compounds with
3,3,5-Trimethylcyclohexanone in Benzene

AlR_3	Ratio of AlR_3/Ketone	% Equatorial Attack
$(CH_3)_3Al$	1.0	100
	2.0	81
	4.0	60
$(C_2H_5)_3Al$	1.0	100
	2.0	89
	4.0	78
$(C_6H_5)_3Al$	1.0	100
	2.0	100
	4.0	100

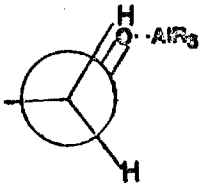
If the reaction were proceeding through the boat conformation, the 3-axial methyl group should have little effect on the stereochemistry. Since this is not the case and for other reasons explored in this

study, the reaction does appear to proceed through the boat conformation.

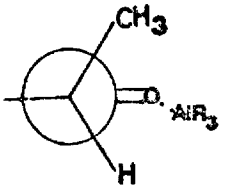
Since the reaction of Me_3Al with 2-methylcyclopentanone in 2:1 ratio also provides attack from the most hindered side of the molecule whereas the reaction in 1:1 ratio does not and since comparable studies with 3-methylcyclopentanone show no change in stereochemistry on changing the Me_3Al:ketone ratio from 1:1 to 2:1, it is clear that the change in stereochemistry between 1:1 and 2:1 ratio is due to the effect that the substituent has at the 2-position in cyclopentanones.

The following explanation satisfies the stereochemistry observed with each ketone. The figures below represent the various orientations of the carbonyl oxygen to substituents on adjacent carbon atoms for each ketone studied. Calculations by Allinger[1] and Fournier[2] give the dihedral angle H_{eq}-C-C-O in cyclohexanones as 3.3 and 5.6°, respectively. The dihedral angle H_{eq}-C-C-O...AlR_3 in the cyclohexanone-AlR_3 complex would be expected to be as large as or larger than in the uncomplexed ketone owing to the steric interaction of the complexed carbonyl with the 2,6-diequatorial hydrogens. Figure G illustrates the angle between the carbonyl oxygen and the hydrogens on adjacent carbons for the 4-<u>tert</u>-butylcyclohexanone-AlR_3 complex. It can be seen that equatorial attack by a second molecule of R_3Al compresses the complexed carbonyl against the equatorial hydrogens in the transition state. On the other hand, axial attack leads to a staggered arrangement between the complexed carbonyl and hydrogens on adjacent carbon atoms. Thus, in the case of the cyclohexanones, this "compression effect" favors attack from the more hindered side of the molecule in the 2:1 R_3Al: ketone ratio. This same effect explains the stereochemistry observed

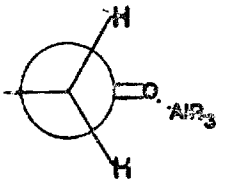
with other ketones. In the case of 2-methylcyclopentanone, Figure H shows the orientation between the carbonyl oxygen and the substituents on the 2- carbon atom and Figure I shows the orientation between the carbonyl oxygen and the substituents on the 3 carbon atom. Trans attack by a second organoaluminum molecule compresses the complexed carbonyl into a methyl group and a hydrogen in the transition state where cis attack complresses the complexed carbonyl between two hydrogens. Thus, the "compression effect" favors attack by a second molecule of organoaluminum compound from the most hindered side of the ketone, the cis side.



(G)



(H)



(I)

This work is discussed in more detail in J. Org. Chem., 38, 2526 (1973).

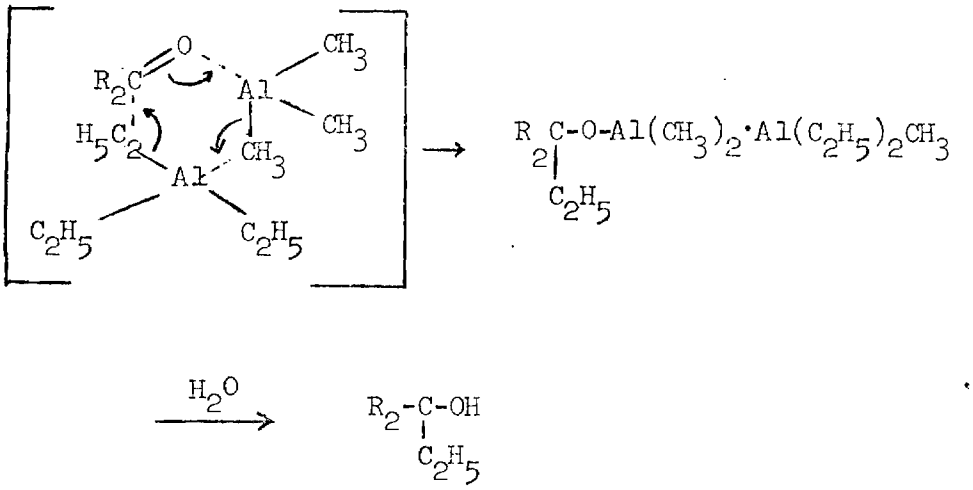
(2) Stereoselective Alkylation of Ketones. Further Studies

One of the most significant observations from this laboratory has been the report of the "compression effect" by which a methyl group can be introduced into certain ketones from the most hindered side in high yield by reaction with $(CH_3)_3Al$.[13] The reaction involves alkylation of the ketone by $(CH_3)_3Al$ in a 2:1 or greater $(CH_3)_3Al$:ketone ratio in hydrocarbon solvent. Unfortunately, the method is limited in those cases where the organoaluminum reagents possess β hydrogens in that reduction products are formed. The possibility of attacking a group other than

CH_3- or C_6H_5- to the most hindered side of 4-t-butylcylcohexanone and 2-methylcyclopentanone (ketones displaying a large compression effect) has been studied. Only a summary of the results are given here due to the large volume of data collected.

Trimethylaluminum was allowed to react with ketone-$Al(CH_3)_3$ and ketone-$AlCl_3$ complexes in benzene solvent. Two possible paths were envisioned for the reaction. If Path I represents the correct discription of the reaction, clean ethylation should be observed since reduction is not possible when the organoaluminum compound possessing β hydrogens is not complexed to the carbonyl oxygen and methylation via internal rearrangement of the $R_2C{=}O\ldots Al(CH_3)_3$ complex is slow.[4]

Path I. Redistribution Slow Compared to Ethylation



Path II. Redistribution Much More Rapid Than Ethylation

A. $2\ R_2C{=}O\cdots Al(CH_3)_3 + 2\ (C_2H_5)_3Al \rightleftarrows R_2C{=}O{\cdot}Al(CH_3)_2C_2H_5 +$

$R_2C{=}O..Al(C_2H_5)_2CH_3 + Al(CH_3)_2C_2H_5 + Al(C_2H_5)_2CH_3$

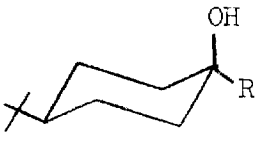
B. $R_2C{=}O..Al(CH_3)_2C_2H_5$ → reduction via β hydrogen transfer

→ methylation + ethylation via attack by $Al(CH_3)_2C_2H_5$ and $Al(C_2H_5)_2CH_3$

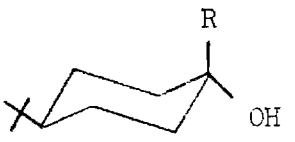
C. $R_2C{=}O\cdots Al(C_2H_5)_2CH_3$ → reduction via β hydrogen transfer

→ methylation + ethylation via attack by $Al(CH_3)_2C_2H_5$ and $Al(C_2H_5)_2CH_3$

A sample of the results involving alkylation of 4-t-butylcyclohexanone shown in the table that follows indicates that Path II correctly describes the system. A mixture of (1:1) $(CH_3)_3Al$:$(C_2H_5)_3Al$ added to the ketone gave essentially the same results as did addition of $(C_2H_5)_3Al$ to $(CH_3)_3Al$·ketone complex. Alkylation products had a high percentage of the equatorial alcohol demonstrating that the primary alkylation path was attack on the organoaluminum:ketone complex rather than internal rearrangement of the complex.



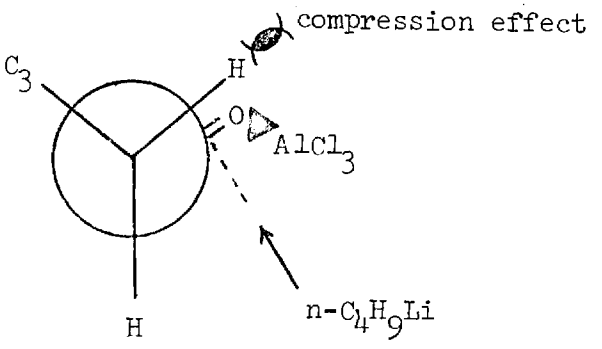
axial alcohol



equatorial alcohol

Organoaluminum compounds such as $(CH_3)_2AlC_2H_5$ and $(C_2H_5)_2AlCH_3$ gave essentially the same alkylation:reduction ratio as did triethylaluminum along with significant percentages of methylation. These results show that methyl and ethyl groups are transferred at about the same rate. Reaction of $(C_2H_5)_2AlCl$ and $C_2H_5AlCl_2$ with 4-t-butylcyclohexanone gave larger percentages of reduction than $(C_2H_5)_3Al$. The same was true in those reactions involving $(C_2H_5)_3Al$ addition to ketone·$AlCl_3$ complexes.

Attempts to introduce n-butyl groups into 4-t-butylcyclohexanone by reaction of n-butyllithium with ketone·$Al(CH_3)_3$ and ketone·$AlCl_3$ complexes were not successful. Alkylation of these complexes gave about the same ratio of axial:equatorial alcohol as did n-butyllithium. Analysis of the results of these reactions indicate that reaction did not occur via the corresponding "ate" complexes, $LiAl(CH_3)_3n\ C_4H_9$ and $LiAlCl_3(n\text{-}C_4H_9)$, since the latter gave a significantly larger percentage of methylation and reduction respectively (see Table).



Reaction of Organoaluminum Compounds, $n\text{-}C_4H_9Li$ and $LiAl(CH_3)_3n\text{-}C_4H_9$
With 4-t-Butylcyclohexanone and 4-t-Butylcyclohexanone·$Al(CH_3)_3$ Complex.[a]

Reagent	Substrate	Reagent Conc., M	Reagent Substrate	Methylation % Total[b]	Methylation % Axial[c] Alcohol	Methylation % Equatorial[c] Alcohol	Alkylation % Total[b]	Alkylation % Axial[c] Alcohol	Alkylation % Equatorial[c] Alcohol	Reduction % Axial[c] Alcohol	Reduction % Equatorial[c] Alcohol	Recovered Ketone %
$(C_2H_5)_3Al$	Ketone	0.204	2.9				74[e]	12	88	25	75	0
$(C_2H_5)_3Al$	Ketone-$Al(CH_3)_3$	0.94	1.0	54	31	71	37[e]	35	65	23	77	2
$(C_2H_5)_3Al_2(CH_3)_3$	Ketone	0.098	1.5	50	11	89	38[e]	12	88	22	78	0
$n\text{-}C_4H_9Li$	Ketone	0.149	1.04				100[f]	67	33	0	0	8.2
$n\text{-}C_4H_9Li$	Ketone-$Al(CH_3)_3$	0.155	1.03	18	53	47	82[f]	79	21			8.0
$LiAl(CH_3)_3n\text{-}C_4H_9$	Ketone	0.156	1.05	86	43	57	24[f]	65	35	0	0	37

a. Complexes formed by organoaluminum reagent addition to ketone followed in 10 to 20 seconds by addition of $n\text{-}C_4H_9Li$

b. Normalized as % methylation + % butylation alcohol + % reduction alcohol = 100%. c. Normalized as % axial alcohol + % equatorial alcohol = 100%. d. Normalized as % total alcohol products + % ketone = 100%. e. Ethylation product.

f. Butylation product.

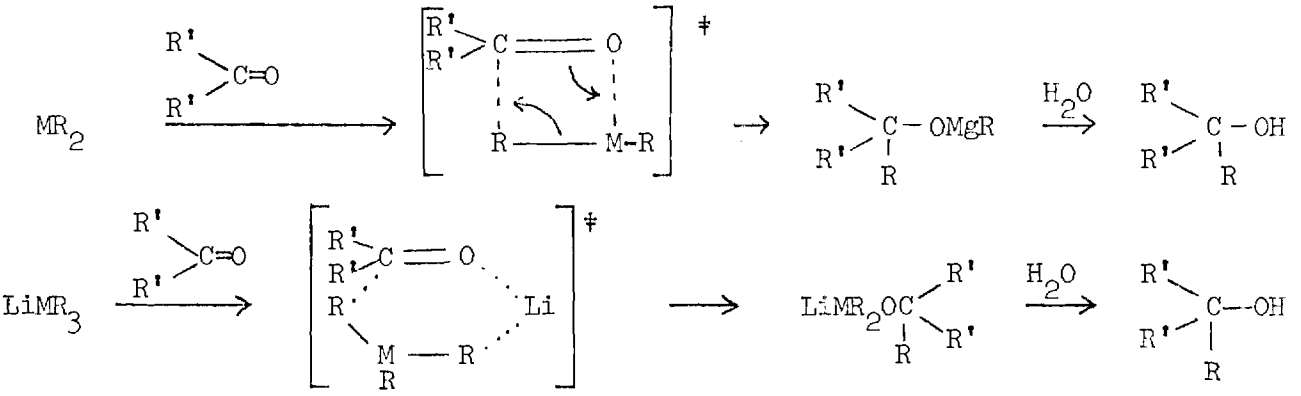
(3) Stereoselective Alkylation of Ketones Using Ate Complexes

Ate complexes are the result of interaction between an electron deficient metal alkyl and a Lewis base.[5] If methyllithium is added to an ether solution of $(CH_3)_3Al$, the ether molecule is replaced by a methyl carbanion to form the ate complex $LiAl(CH_3)_4$. In general, the tendency towards ate complex formation and the stability of the complex depends to a large degree on the particular metals involved and to a lesser degree on the ligand size and charge. For example, the tendency of the adducts $LiM(C_6H_5)_3$ to dissociate into phenyl lithium and $M(C_6H_5)_2$ increases in the order:

$$LiBe(C_6H_5)_3 < LiZn(C_6H_5)_3 < LiMg(C_6H_5)_3 < LiCd(C_6H_5)_3 < LiHg(C_6H_5)_3$$

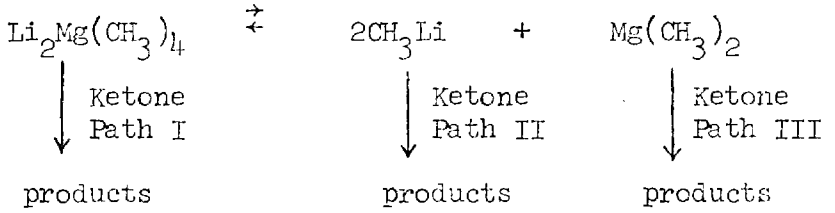
In general, the smaller the central metal atom, the more stable the adduct.

No reports concerning either the mechanism or stereochemistry of ate complex addition to ketones has appeared in the literature. Since the central metal atom of ate complexes such as $LiAl(CH_3)_4$ or $Li_2Zn(CH_3)_4$ do not have available orbitals for complexation with a carbonyl group as do $(CH_3)_3Al$ and $(CH_3)_2Zn$, there is reason to believe that the mechanism and hence stereochemistry of reaction should be different. In addition it was felt that since lithium salts are capable of complexing with carbonyl compounds, possibly ate complexes of the type $Li_nM(CH_3)_{2+n}$ might react by complexation of the lithium atom with the carbonyl oxygen atom.



Such possibilities in addition to recent reports concerning the composition of ate complexes in solution[6] have prompted us to investigate these compounds as stereoselective alkylating agents.

The stereochemistry of reaction of ate complexes of magnesium, boron and zinc with several ketones is illustrated in the following table. The stereochemistry of addition of CH_3Li, $(CH_3)_2Mg$ and $(CH_3)_2Zn$ is also shown for comparison. The data in the following table represents only a fraction of the total data collected, but demonstrates all factors discussed. The principle feature of all these reactions is that attack by the ate complex occurs predominantly at the less hindered side of the carbonyl group in every case. In addition, the ratio of isomeric alcohols obtained by alkylation with ate complexes is essentially the same as that found for alkylation by the separate reagents which compose the ate complex. Thus, the following general reaction scheme, employing $Li_2Mg(CH_3)_4$ as a specific example, can be written for ate complex addition to ketones.



Reaction of Ate Complexes of Boron, Magnesium and Zinc with Ketones in Diethyl Ether

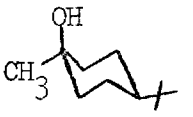
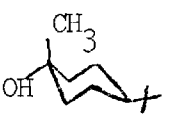
Reagent	Initial Concentration(M)	Ratio Reagent:Ketone	Ketone	% Axial Alcohol 	% Equatorial Alcohol 
Li	0.76	4.0	4-t-butyl cyclohexanone	65	35
$_3)_2Mg$	0.44	4.0	"	70	30
$_3)_2Zn$	0.20	4.0	"	no reaction	
$(CH_3)_4$	0.20	1.0	"	no reaction after 4 day	
"	0.20	3.0	"	no reaction after 4 day	
"	0.20	5.0	"	67[b]	33[b]
$g(CH_3)_3$	0.22	1.0	"	69	31
"	0.36	4.0	"	70	30
$Mg(CH_3)_4$	0.14	2.0	"	69	31
$Mg(CH_3)_5$	0.14	2.0	"	71	29
$g(C_6H_5)_2CH_3$	0.10	1.0	"	65[c]	35[c]
$n(CH_3)_3$	0.23	1.0	"	64	36
"	0.37	4.0	"	70	30
$Zn(CH_3)_4$	0.14	2.0	"	68	32
$Zn(CH_3)_5$	0.14	2.0	"	69	31
$(CH_3)_2OtC_4H_9$[t]	0.027	4.0	"	71	29
$C_8H_{17})_3C_3H_7Mg(CH_3)_2Br$	0.132	3.0	"	75	25

Table I Continued

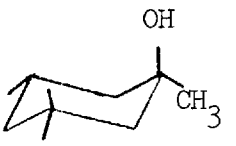
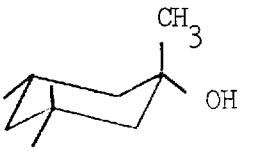
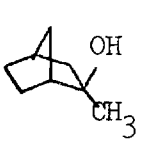
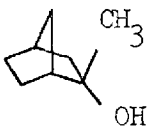
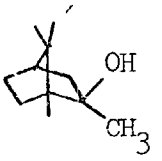
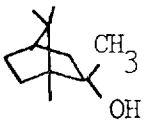
gent	Initial Concentration (M)	Ratio Reagent:Ketone	Ketone	% Axial Alcohol[a]	% Equatorial Alcohol[a]
					
;Li	0.19	1.0	3,3,5-Trimethyl-Cyclohexanone	100	0
$I_3)_2Mg$	0.21	1.0	"	100	0
$I_3)_2Zn$	0.16	1.0	"	no reaction	
$Mg(CH_3)_3$	0.36	4.0	"	100	0
;$Mg(CH_3)_4$	0.21	1.0	"	100	0
;$Mg(CH_3)_5$	0.27	4.0	"	100	0
$Zn(CH_3)_3$	0.25	1.0	"	100	0
;$Zn(CH_3)_4$	0.30	4.0	"	100	0
;$Zn(CH_3)_5$	0.25	4.0	"	100	0
					
				% exo-alcohol	% endo-alcohol
Li	0.80	4.0	Norcamphor	5	95
$3)_2Mg$	0.46	3.0	"	5	95
$3)_2Zn$	0.28	3.0	"	no reaction	
$Mg(CH_3)_3$	0.33	3.0	"	5	95
$Mg(CH_3)_4$	0.28	1.0	"	5	95
$Mg(CH_3)_5$	0.27	3.0	"	5	95
$n(CH_3)_3$	0.32	1.0	"	5	95
$Zn(CH_3)_4$	0.32	3.0	"	5	95
$Zn(CH_3)_5$	0.27	3.0	"	5	95

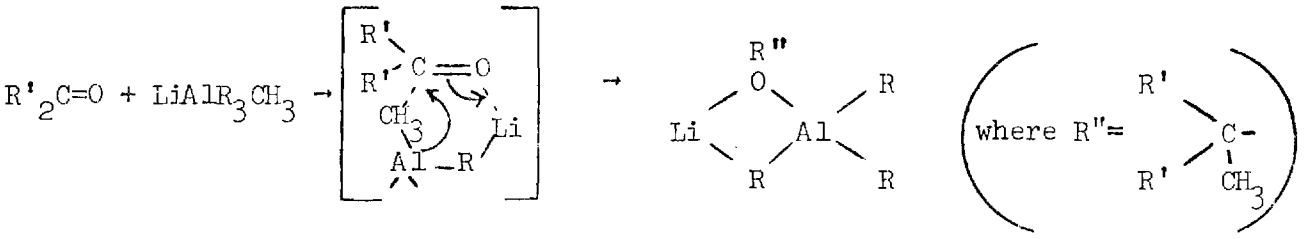
Table I Continued

;ent	Initial Concentration (M)	Ratio Reagent:Ketone	Ketone	% Exo Alcohol[a] 	% Endo Alcohol[a] 
;i	0.23	1.0	Camphor	99	1
;)$_2$Mg	0.51	4.0	"	99	1
;)$_2$Zn	0.22	4.0	"	no reaction	
;(CH_3)$_3$	0.37	4.0	"	99	1
;g(CH_3)$_4$	0.22	1.0	"	99	1
;g(CH_3)$_5$	0.27	4.0	"	99	1
;(CH_3)$_3$	0.39	4.0	"	99	1
;n(CH_3)$_4$	0.22	1.0	"	99	1
;n(CH_3)$_5$	0.26	4.0	"	99	1

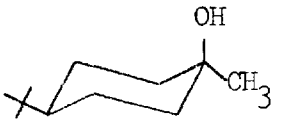
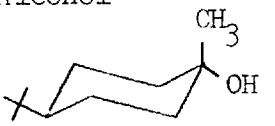
Normalized as % Axial(Exo)Alcohol + % Equatorial(Endo)Alcohol = 100%. [b.] Reaction ;ied out in refluxing benzene for 3 days. Total yield of alcohol products was 48%. Reaction ;enzene at room temperature was not carried out due to low solubility of $LiB(CH_3)_4$ in ;ene. [c.] Methylation products.

The ate complexes of aluminum are considered separately due to the unusual stereochemistry observed in their reaction with 4-t-butylcyclohexanone (following tables). Lithium tetramethylaluminate alkylates 4-t-butylcyclohexanone predominantly from the most hindered axial side in diethyl ether, tetrahydrofuran, and dimethoxyethane. This is an unusual result because all reagents except excess $(CH_3)_3Al$ in benzene and $(CH_3)_2Zn$ and $(CH_3)_2Cd$ in the presence of magnesium halide[7] attack this ketone from the less hindered equatorial side. The percent equatorial alcohol formed (about 58%) is essentially the same in all solvents and is independent of reactant concentrations and ratios. In the more basic solvents, a greater amount of ketone is recovered indicating a larger percentage of enolization. The reason for the unusually high percentage of axial attack in these cases is not immediately obvious

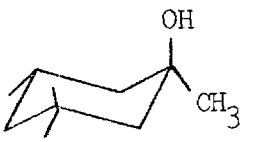
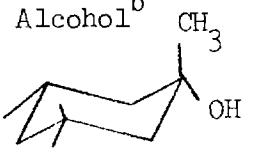
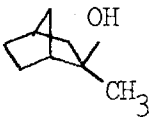
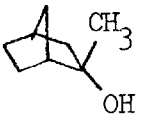
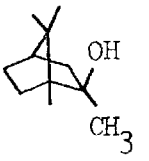
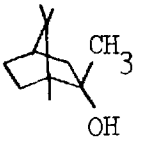
The stereochemistry of addition of aluminum ate complexes to 4-t-butylcyclohexanone in benzene is illustrated in the table below. In 1:1 reactant ratio $LiAl(CH_3)_4$ gives slightly less axial attack on 4-t-butylcyclohexanone than in polar solvents (58%). In addition, the observed isomer ratio of the products is dependent on reactant ratio with the percentage of axial attack increasing as the ate complex:ketone ratio increases. If coordination of the ketone takes place at lithium, it is possible to draw a reasonable transition state for the reaction.



Reaction of Ate Complexes of Aluminum with Ketones in Polar Solvents[a]

eagent	Initial Concentration (M)	Ratio Reagent:Ketone	Ketone	% Axial Alcohol[b] 	% Equatorial Alcohol[b] 
iAl$(CH_3)_4$	0.15	1.0	4-t-butyl-cyclohexanone	42	58
"	0.21	4.0	"	42	58
"	0.18	1.0	"	44[c]	56[c]
"	0.37	4.0	"	43[c]	57[c]
"	0.39	1.0	"	43[d]	57[d]
"	0.63	4.0	"	44[d]	56[d]
iAl$(i\text{-}C_4H_9)_3CH_3$	0.10	1.0	"	18[e]	82[e]
"	0.30	3.0	"	31[e]	69[e]
"	0.355	1.0	"	31[e]	69[e]
"	0.461	3.0	"	33[e]	67[e]
$n\text{-}C_8H_{17})_3C_3H_7NAl(CH_3)_3Br$	0.044	1.0	"	81	19
"	0.132	3.0	"	77	23

Continued

Reagent	Initial Concentration (M)	Ratio Reagent:Ketone	Ketone	% Axial Alcohol[b] 	% Equatorial Alcohol[b] 
$iAl(CH_3)_4$	0.40	1.0	3,3,5-Trimethyl-cyclohexanone	100	0
"	0.54	4.0	"	100	0
				 Exo Alcohol	 Endo Alcohol
$iAl(CH_3)_4$	0.19	1.0	Norcamphor	5	95
"	0.61	4.0	"	5	95
				 Exo Alcohol	 Endo Alcohol
$iAl(CH_3)_4$	0.36	1.0	Camphor	99	1
"	0.58	4.0	"	99	1

Diethyl ether unless otherwise noted. [b] Normalized as % axial(exo)alcohol + % equatorial endo)alcohol = 100%. [c] Tetrahydrofuran. [d] Dimethoxyethane. [e] Methylation product. The jor product of these reactions is reduction (66 to 75%). In all cases the reduction product is composed of 48% axial alcohol and 52% equatorial alcohol.

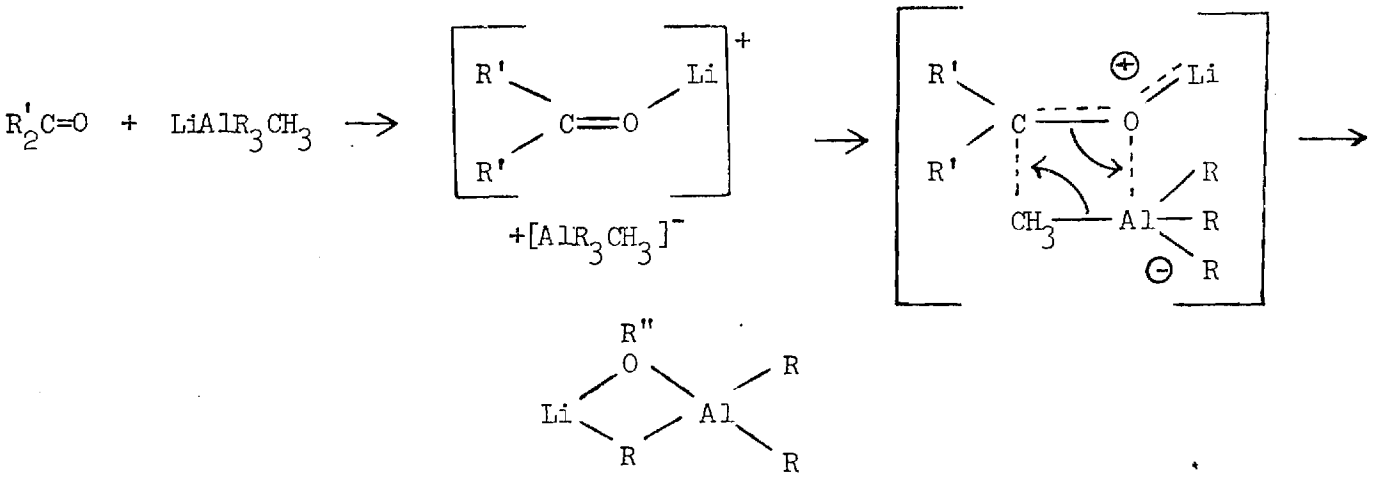
Reaction of Ate Complexes of Aluminum with

4-t-Butylcyclohexanone in Benzene

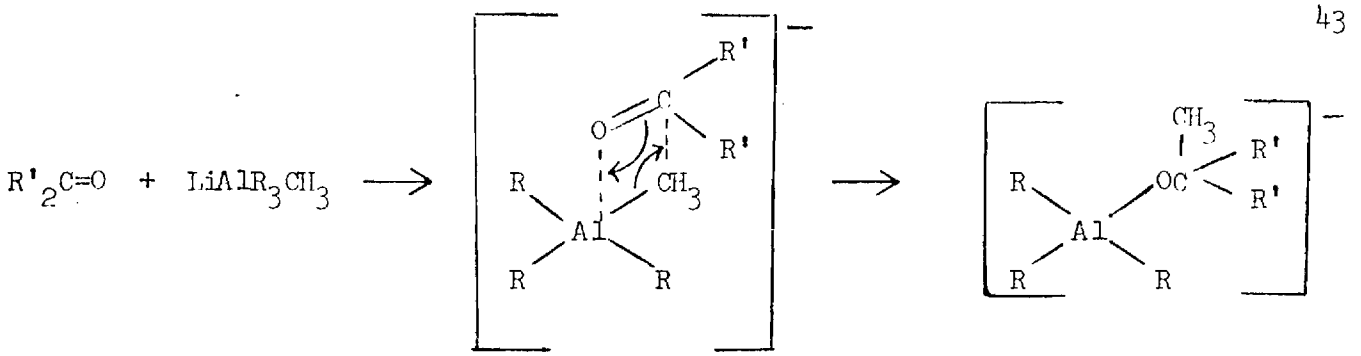
ent	Initial Concentration (M)	Ratio Reagent:Ketone	% Axial Alcohol[a]	% Equatorial Alcohol[a]
$(CH_3)_4$	0.012	1.0	52	48
	0.012	4.0	42	58
$(i\text{-}C_4H_9)_3CH_3$	0.085	1.0	trace[b]	0[b]
	0.26	3.0	0[b]	0[b]
$8^{H}17)_3C_3H_7NAl(CH_3)_3Br$				
	0.044	1:1	75	25
	0.132	3:1	76	24

Normalized as - % axial alcohol + % equatorial alcohol = 100%. [b.] Methylation product. The only product of these reactions is reduction with no recovered ketone. The reduction product was composed of 39-31% axial alcohol and 61-69% equatorial alcohol at the low and high ratios respectively.

Coordination of the carbonyl oxygen atom by lithium followed by a rate determining carbanionic attack at the carbonyl carbon atom is somewhat reminiscent of the reaction of ketones with R_3Al compounds in 1:2 ratio where the first molecule coordinates the carbonyl oxygen and the second attacks the carbonyl carbon. The fact that the stereochemistry of ate complex alkylation reveals predominant axial attack rather than the usual 30:70 (axial:equatorial) ratio observed by those reactions that proceed through a 4-cetner transition, lends some support to the proposed mechanism. It is not necessary that the transition state be cyclic; indeed, one could picture a consecutive bimolecular reaction in which the lithium ion complexed carbonyl group is then attacked by the tetraalkylaluminate ion.



It is possible that coordination takes place through the aluminum atom rather than lithium; however, solvation studies on $LiAl(CH_3)_4$ with ether solvents indicates that the ether is attached to lithium and not aluminum and furthermore the observed stereochemistry is not consistent with this suggestion.



Similar mechanistic suggestions could be made to explain the reduction reactions; however there is even less justification than exists for the alkylation reactions to discuss these reactions at this time.

D. Publication of Work Since the Last Report Period.

(NSF Grant GP-31550X2, $98,846 for 3 years is the sole source of support for all organometallic work done in our group and reported in the ensuing publication list).

1. E. C. Ashby and Simon H. Yu, "Composition of Grignard Compounds. VIII. Alkylmagnesium Fluorides", J. Organometal. Chem., 29, 339 (1971).

2. E. C. Ashby and Simon H. Yu, "Alkylmagnesium Fluorides. II. Preparation and Properties," J. Org. Chem., 36, 2123 (1971).

3. J. Laemmle, E. C. Ashby and H. M. Neumann, "Organometallic Reaction Mechanisms. V. The Mechanism of Dialkylmagnesium Addition to Ketones," J. Amer. Chem. Soc., 93, 5120 (1971).

4. E. C. Ashby, J. Laemmle and H. M. Neumann, "Direct Evidence for the Reactive Species and Their Reaction Orders in the Addition Reaction of Methyl Bromide Grignard to 2-Methylbenzophenones," J. Amer. Chem. Soc., 93, 4601 (1971).

5. E. C. Ashby and Simon H. Yu, "Stereoselective Alkylation Reactions. I. Organomagnesium and Organoaluminum Addition to 4-t-Butylcyclohexanone. Unusual Stereoselectivity Involving Trimethylaluminum Alkylation in Benzene," J. Org. Chem., 37, 1918 (1972).

6. E.C. Ashby, J. Laemmle, and H. M. Neumann, "Organometallic Reaction Mechanisms. VIII. The Mechanism of Methylmagnesium Bromide Addition to 2-Methylbenzophenone," J. Amer. Chem. Soc., 94, 5421 (1972).

7. E. C. Ashby, and J. Nackashi, "Alkoxy-Alkyl Mixed Bridged Organomagnesium Compounds," J. Organometal. Chem., 35, C1 (1972).

8. E. C. Ashby, "The Composition of Grignard Compounds in Ether Solvents as Inferred from Molecular Association and NMR Studies. Relevance of Grignard Compound Composition to Reaction Mechanisms and Stereochemistry," Bull Soc., Chemie de France, 2133 (1972).

9. E. C. Ashby, Li-Chung Chao, and H. M. Neumann, "Organometallic Reaction Mechanisms. XII. The Mechanism of Grignard Addition to Benzonitriles," J. Amer. Chem. Soc., 94, 4896 (1972).

10. H. M. Neumann, J. Laemmle, and E. C. Ashby, "Organometallic Reaction Mechanism. IX. Evidence for the Detailed Nature of the Alkyl Transfer Step in the Addition Reaction of Trimethylaluminum with Benzophenone," J. Amer. Chem. Soc., 95, 2597 (1973).

11. E. C. Ashby, H. M. Neumann, F. W. Walker, J. Laemmle, and Li-Chung Chao, "Organometallic Reaction Mechanisms. X. Concerning the Effect of Magnesium Metal Purity and the Method of Preparation of Grignard Reagents on Reaction with Ketones and Nitriles," J. Amer. Chem. Soc., 95, 3330 (1973).

12. E.C. Ashby, Li-Chung Chao, and H.M. Neumann, "Organometallic Reaction Mechanism. XI. The Mechanism of Dimethylmagnesium Addition to Benzonitriles," J. Amer. Chem. Soc., 95, 5186 (1973).

13. J. Laemmle, E.C. Ashby and P.V. Roling, "Stereoselective Organometallic Alkylation Reactions. II. Organomagnesium and Organoaluminum Addition to Ketones Having Varied Steric Requirements. A New Concept of Stereochemical Control," J. Org. Chem., 38, 2526 (1973).

14. G.E. Parris and E.C. Ashby, "The Composition of Grignard Compounds. IX. The Structure and Solution Composition of Cyclopentadienylmethylmagnesium in Benzene and Ether Solvents," J. Organometal. Chem., 72, 1 (1974).

15. E.C. Ashby and John Nackashi, "The Preparation of Organomagnesium Flourides by Organometallic Exchange Reactions," J. Organometal. Chem., 72, 6 (1974).

16. E.C. Ashby, H.M. Neumann and J. Laemmle, Accounts of Chem. Res., 7, 272 (1974).

17. E.C. Ashby, Li-Chung Chao and J. Laemmle, "Stereoselective Organometallic Alkylation Reactions. III. "Ate" Complex Addition to Cyclic and Bicyclic Ketones," J. Org. Chem., 39, 3258 (1974).

18. E.C. Ashby and George Heinsohn, "Transition Metal Catalyzed Conjugate Methylation of α,β-Unsaturated Ketones by Trimethylaluminum and Lithium Tetramethylaluminate," J. Org. Chem., 39, 3297 (1974).

19. E.C. Ashby and Tom Weisemann, "Transition Metal Catalyzed Single Electron Transfer in Grignard Reagent Addition to Ketones," J. Amer. Chem. Soc., 96, 7117 (1974).

Publications in Press

1. E.C. Ashby and J. Laemmle, "Stereochemistry of Organometallic Compound Addition to Ketones," Chem. Rev., (in press).

2. E.C. Ashby, Irene Lopp and Jerry D. Buhler, "Mechanisms of Grignard Reactions with Ketones: Polar vs Single Electron Transfer Pathways," J. Amer. Chem. Soc., (accepted for publication).